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Abstracts

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Nephroptosis and hypertension. *D. de Zeeuw, A. J. M. Donker, J. Burema, G. K. van der Hem, and E. Mandema. Department of Medicine, State University of Groningen, Groningen, the Netherlands.* An abnormal renal mobility in the upright position (nephroptosis) is observed in 20% of women, predominantly on the right side. Fibromuscular dysplasia (FMD) of the renal artery is also observed mainly in women on the right side. The sex-dependency and the equal incidence with which the right kidney is affected by both phenomena suggest an association between FMD and nephroptosis. Moreover, a relation is suspected between renal mobility and kidney perfusion. In order to evaluate nephroptosis in its relation to FMD and/or hypertension, the renal mobility was studied in 14 patients with a FMD of the renal artery, in 102 patients with essential hypertension, and in 89 patients with a normal blood pressure, by comparing the patients' recumbent and upright positions on film made during i.v. pyelography. The degree of mobility (m) was expressed in millimeters. It was found that, in contrast to males, females often showed a marked renal mobility and that the renal mobility correlated with the blood pressure ($r = 0.50$, $N = 105$, $P < 0.001$). Female patients with hypertension (diastolic pressure ≥ 100 mm Hg) showed a distinct renal mobility on the right side ($N = 63$, m = 6.29 cm, SD = 1.99 cm). Normotensive females had a significantly lower ($P < 0.001$) mean right renal mobility ($N = 42$, m = 3.42 cm, SD = 2.12 cm). The difference was not significant on the left side ($P > 0.10$). The blood pressure-renal mobility relation was confirmed by a multivariate regression analysis. Moreover, the difference in right kidney mobility remained significant ($P < 0.001$) after matching the hypertensives and controls with respect to age, body weight, body height, parity, and medication. Fibromuscular dysplasia of the renal artery was accompanied by an impressive renal mobility on the side involved (8.6 ± 1.7 cm on the right side and 6.8 ± 2.8 cm on the left side). The results of this study indicate that in women nephroptosis contributes, directly and/or indirectly, to the development of high blood pressure.

Antiproteinuric effect of indomethacin in rats with experimental extramembranous (Heymann-type) nephritis. *F. W. J. Gribnau, H. L. M. Siero, G. J. Fleuren, Ph. J. Hoedemaeker, and P. G. A. B. Wijdeveld. Pharmacological Institute, and Division of Nephrology of Department of Medicine, University Nijmegen, and Department of Pathology, University Groningen, The Netherlands.* Indomethacin is known to have an immediate and reversible antiproteinuric effect in the human nephrotic syndrome. The purpose of this work was to study whether this effect could likewise be realized in an animal experimental model. In inbred male PVG/C rats, extramembranous glomerulopathy was induced by repeated i.p. immunization with a diazotized Wistar rat kidney antigen. The experimental disease is associated with proteinuria (400 to 900 mg/rat/day) and hypalbuminemia (about 26% of healthy controls). There is no impairment of GFR; natriuresis is normal and no edema occurs. Indomethacin given at different times in the course of the disease (daily doses of 2×0.15 to 2×0.60 mg/rat) failed to reduce protein excretion in animals receiving standard feed (sodium content, 191μEq/g of feed). When animals on a salt-restricted diet (5μEq/g) were given the drug (2×0.60 mg daily), an immediate decrease of proteinuria to about 60% of control values was observed. The effect was reversible after discontinuation of treatment. In concentrations existing in plasma at the dose given in these experiments, indomethacin inhibits the synthesis of prostaglandins. Therefore, theoretically, indomethacin effects are likely to occur, especially in situations with increased prostaglandin synthesis and/or enhanced activity of substances counteracting prostaglandins' effects, e.g., angiotensin. From these considerations, one might speculate that only superimposing salt restriction on the hypalbuminemia in these animals produces sufficiently high angiotensin activity, probably connected with sufficiently high prostaglandin synthesis rate, needed to give therapeutic effects of indomethacin on kidney function.

Effects of indomethacin on the course of extramembranous (Heymann-type) glomerulonephritis in rats. *F. W. J. Gribnau, H. L. M. Siero, G. J. Fleuren, Ph. J. Hoedemaeker, and P. G. A. B. Wijdeveld. Pharmacological Institute, and Division of Nephrology of the Department of Medicine, University Nijmegen, and Department of Pathology, University Groningen, The Netherlands.* Opinions differ as to whether indomethacin favourably influences the course of human chronic glomerulonephritis. Therefore, we have studied the effect of indomethacin on the natural course of an experimental glomerulonephritis in rats. Inbred male PVG/C rats were immunized (12 injections i.p. in six weeks) with a diazotized Wistar rat kidney antigen and divided into indomethacin-treated and control groups. For periods up to 500 days, proteinuria, endogenous creatinine clearance (ECC), and renal morphology (light microscopy, immunohistochemistry, and electron microscopy) were studied. The disease was found to be associated with proteinuria (400 to 900 mg/rat/day), hypalbuminemia (about 26% of controls) and hypercholesteremia (10 mmoles/liter). ECC remained normal, as did renal capacities for sodium excretion and retention. In animals kept on standard feed (191μEq of Na/g of feed), no edema occurred. From week four on, a nonproliferative glomerulonephritis started, with characteristic "spikes," granular pattern of immunofluorescence (IgG and C3), subepithelial electron-dense deposits which increased in size and irregularity, and thickening of the glomerular basement membrane (GBM). From week 33 on, deposits gave place to electron-microscopically empty "holes" in the GBM. About week 75, these holes had been filled with GBM substance. Only if the drug was given during the phase of immunization, indomethacin dose-dependently reduced the proteinuria by 26% (dose, 0.30 mg/rat/day) to 45% (dose, 0.60 mg/rat/day). ECC was not influenced. Change of the morphologic features was only seen in electron microscopy, and the differences seemed to be of minor importance. In indomethacin-treated animals, subendothelial electron-dense deposits were observed, likewise seen in nonimmunized indomethacin-treated controls. Indomethacin seemed to accelerate the electron microscopic characteristics of the disease in the first 22 weeks, and later on in the disease, to reduce the number of optically empty spaces in the GBM. Although findings in one experimental nephritis in one animal species are admissible as evidence, the reported results lend no support to the view that long-term indomethacin treatment might be beneficial in chronic glomerulonephritis. Possibly, situations analogous to the phase of immunization in these experiments, in this respect, are exceptions.

Effect of immediate aortic constriction on sodium excretion during acute extracellular volume expansion in the dog. *N. Lameire, M. A. Walterloos, I. Becaus, S. Ringoir. Nephrological Division, University Hospital, De Pintelaan, Ghent, Belgium.* Studies in the rat have indicated that aortic constriction (AC) prior to expansion of the extracellular volume (ECV) prevents the natriuretic response normally seen in this setting. These findings are taken as evidence against the role for an extrarenal natriuretic hormone. In order to evaluate this finding in the dog, clearance studies were performed to compare the effect of AC prior to and after ECV expansion of 7.5% body wt with 0.9% saline. Two groups were studied: *Group 1. Delayed clamp studies (N = 7).* After hydropenic clearances, saline was given for 40 min, and the renal perfusion pressure (RPP) was reduced to a mean of 80 mm Hg while the saline was continued. *Group 2. Immediate clamp studies (N = 8).* After hydropenic clearances, RPP was decreased to 75 mm Hg followed by saline-loading. In both groups, clearance collections were obtained 60 min after the initiation of the saline-looking. In group 1, total kidney glomerular filtration rate (GFR) and para-aminohippurate clearance remained constant (21.7 vs. 18.8 and 60 vs. 54 ml/min/kidney; $P > 0.05$). Absolute and fractional sodium excretion increased from 29.6 to 63.0μEq/min ($P < 0.05$) and from 1.08 to 2.58%, respectively ($P < 0.02$). In group 2, total kidney GFR decreased from 81 to 49 ml/min/kidney ($P < 0.01$). Both absolute and fractional sodium excretion, however, increased from 30.1 to 57.1μEq/min ($P < 0.05$) and from 0.80 to 1.85% ($P < 0.02$), respectively. The arterial hematocrit dropped from 43 to 25% ($P < 0.01$) and from 40 to 26% ($P < 0.01$) in groups 1 and 2, respectively. After release of the AC, fractional sodium excretion increased to 10.5% ($P < 0.001$) in both groups. These results indicate that immediate AC does not obviate the natriuretic response to saline-loading in the dog and, therefore, does not permit us to exclude an extrarenal "natriuretic hormone" factor as mediator of the increased natriuresis after acute ECV expansion.

Studies about the pathogenesis of the hemolytic-uremic syndrome (HUS). *L. Monnens, I. Lambooy, P. van Wieringen, J. Bakkeren. St. Radboud Ziekenhuis, Kindernefrologie, Nijmegen.* The pathogenesis of HUS remains still partly obscure. In two different ways we have tried to elucidate its pathogenesis. First, endotoxin was sought in the peripheral circulation of children with HUS, and second, we have tried to measure circulating endothelial cells in children and also in the experimental animal. Endotoxin has all the qualities of being the prime mediator of acute intrinsic renal failure. In HUS, endotoxinemia may arise from the flora of the damaged bowel. The limulus assay is generally accepted as being highly specific for gram-negative endotoxins, as well as being the most sensitive test at present. In eighteen children with HUS, we were unable to detect circulating endotoxin by using the limulus lysate assay. Ten children with proven gram-negative septicemia yielded positive limulus assays. All normal control children showed negative limulus assays. Some evidence is available in favor of the primary character of the damage to the endothelium of the arterioles and capillaries in HUS. In four children with HUS, tested immediately after admission, circulating endothelial cells could not be demonstrated. To evaluate these results, we induced the generalized Shwartzman reaction by liquoid in the rat. Liquoid has a direct injurious effect on endothelium. We demonstrated that the number of circulating endothelial cells in this experimental model depended not only on the dose of injected liquoid, but also on the time passed after injection. A huge number of circulating endothelial cells was seen one hour after the injection of liquoid. Twenty-four hours after the injection, circulating endothelial cells were no longer detected. If in the child with HUS, the number of circulating endothelial cells was comparable with the number of these cells in the rat four hours after liquoid injection, the endothelial cells would have been detected. The negative findings in children with HUS can be explained by the fact that either endothelial lesions are not extensive or, and this is probably the best explanation, that these cells have already disappeared.

Serum protein-binding of phenylbutazone during the course of acute renal failure. *M. Mussche, F. Belpaire, M. Bogaert, S. Ringoir. Department of Internal Medicine, Nephrological Division, and Heymans Institute of Pharmacology, University Hospital, De Pintelaan, Ghent, Belgium.* Decreased drug serum protein (SPB) has been described in patients with chronic renal failure. Scanty information exists about the evolution of SPB during the course of human acute reversible renal failure, SPB of ^{14}C-phenylbutazone was studied in five patients with acute renal failure: in four of them, hemodialysis was temporarily required. For determination of SPB, an equilibrium dialysis method was used. During the oliguric period, a very low SPB (mean of 84%) was observed. During recovery from acute renal failure, SPB progressively normalized in all to > 94%. This problem was further investigated in an animal model of acute toxic renal failure. The latter was induced in rabbits by i.v. administration of uranyl nitrate (UN) in a dose of 2 mg/kg. SPB of phenylbutazone decreased in parallel with deterioration of renal function, as estimated by a blood urea level (from control value of 95% to 80–85% for SPB and from a control value of 0.3 g/liter to 3-5 g/liter for blood urea). Normalization of SPB was observed in two rabbits with recovery of their renal failure, while the others died in renal failure. The decreased SPB in uremic rabbits could be explained by a significant decrease in binding constant (K), since a normal number of binding sites (N) as compared to controls was observed (5 control rabbits: K ($M^{-1} \times 10^{-3}$) = 49.14 ± 5.22, N = 1.66 ± 0.11; uremic rabbits: K = 19.62 ± 3.26, N = 1.41 ± 0.07). *Conclusion: 1)* The decreased drug serum protein-binding, observed in both human and animal models of acute renal failure, is reversible with recovery of the renal function. *2)* These findings may be important in the therapeutic drug management of patients with acute renal failure.

"Upright hyperkalemia": A manifestation of hyporeninism in young patients with glomerulonephritis (GN). *J. P. Rado, T. A. Simatupang, P. Boer, and E. J. Dorhout Mees. Department of Nephrology and Hypertension, University Hospital, Utrecht, The Netherlands.* Hyperkalemia is the most conspicuous abnormality in selective hypoaldosteronism, which may be due to defective biosynthesis of aldosterone, or insufficient release of renin, or a combination of both. Selective hypoaldosteronism due to hyporeninism has been reported mostly in older people. We report two young patients (the first, aged 29 yr, with mesangial proliferative "immunocomplex" GN; the second, aged 18 yr, with Alport's disease) with stable chronic renal failure and hyperkalemia not proportional to the moderate degree of renal insufficiency (creatinine clearances varied between 15 to 25 ml/min). Hyperkalemia (serum potassium [S_K] range, 5 to 7.3 nmoles/liter) was observed in both subjects in the outpatient situation during a normal sodium, low potassium diet, with or without Resonium treatment. Repeatedly, after admission to the hospital, high S_K fell to the approximately normal level ($P < 0.01$), even during a normal dietary potassium intake (80 mmoles/day), irrespective of the dietary sodium content. In the hospital, the patients were not confined to bed, but had the restricted activity of a normal hospital life. Blood sampling was done early in the morning in the recumbent position or shortly after awakening. Adrenal function was normal as evaluated by adrenocorticotropic hormone (ACTH) stimulation (there was a normal increase in plasma cortisol and plasma aldosterone levels). Intrinsic tubular potassium excreting capacity was not defective, as in both patients potassium excretion could exceed filtered potassium. Hyporeninism was diagnosed on the basis of unresponsiveness of plasma renin activity (PRA) to the upright posture. PRA (during sodium [Na] restriction) was 74.2 ng of angiotensine I (AI) (100 ml/hr in the first patient, and 155 ng of AI/100 ml/hr in the second one) (normal, 280 ng of AI/100 ml/hr. Urinary aldosterone excretion during normal Na intake was 0.9 mEq/24 hr in the first and 13.4 mEq/24 hr in the second patient, increasing only slightly to 4 mEq/24 hr and 23.2 mEq/24 hr, respectively, during a 50 mmole Na diet. (Normal: <20 mEq on normal Na intake, and > 25 mEq on low Na intake.) Further abnormalitis, in addition to hyporeninism, in both patients were: *1)* a disturbed cellular uptake of potassium, and *2)* an altered tubular response to a pharmacologic dose of aldosterone. Details of

these will be presented elsewhere. During dietary Na restriction, both patients proved to be capable of excreting a normal potassium load, while maintaining normal S_K levels. After discharge from the hospital on the same Na restricted diet, S_K levels increased again slightly, but remained definitely lower than during the preadmission outpatient period ($P < 0.01$). Increase in Na intake was again followed by an increase in S_K levels. In our young, hyporeninemic, hypoaldesteronemic patients with GN, hyperkalemia was significantly ($P < 0.01$) more pronounced in the outpatient situation (especially during unrestricted Na intake) in which the patients had to deal with the activities of normal daily life mostly in the upright position, as contrasted to the restricted activity and recumbency in hospital life. We believe that *insufficient physiologic adjustments in response to the upright position are instrumental in causing "upright hyperkalemia."* The "spontaneous" fall in S_K levels after admission of these patients to the hospital may be deceptive and lead to underestimation or neglection of the problem.

Effects of indomethacin on glomerular permeability. *R. G. W. L. Tiggeler and P. G. A. B. Wijdeveld. Division of Nephrology, Department of Internal Medicine. Sint Radboud Ziekenhuis, Nijmegen, The Netherlands.* Indomethacin reduces proteinuria in glomerular leakage. There is no good explanation for this effect. We studied whether it could be explained by an influence on glomerular permeability. Parameters were the fractional clearance of ^{125}J-labelled polyvinylpyrollidone (C_{PVP}) and the clearance quotient for IgG and albumin (selectivity index, SI). C_{PVP} was studied in 24, SI in 33 patients with a nephrotic syndrome. Measurements were performed in the untreated condition, and on day five of treatment, with indomethacin (150 mg orally, divided over three doses). The C_{PVP} in untreated condition showed the three types described previously: C_{PVP} as in normals (3 patients); C_{PVP} normal for molecules < 40 Å and increased for molecules > 40 Å (5 patients); C_{PVP} lowered for molecules < 40 Å and increased for molecules > 40 Å (16 patients). Indomethacin did not change $C_{PVP} < 40$ Å. In 18 out of 21 patients with increased $C_{PVP} > 40$ Å, a reduction was found with indomethacin therapy. The effect was statistically significant. In the untreated condition, SI was < 0.22 in 16, and > 0.22 in 17 patients. In both groups, SI was reduced after indomethacin administration in 10 patients, and remained equal or increased in the others. Of the 33 patients, 23 were on a sodium intake < 10 mmoles/day. In this group, SI went down in 16. In the nonsodium-restricted group, SI went down in three patients. Statistically, the conclusion that indomethacin would lower SI was not justified. Neither the results with C_{PVP} nor those with SI could be correlated with underlying glomerular disease, endogenous creatinine clearance, level of proteinuria, or degree of hypalbuminemia. There was no correlation either with the effect of indomethacin on proteinuria or, if present, on endogenous creatinine clearance. It can be concluded that, if a nephrotic syndrome is associated with an increased permeability for inert macromolecules with molecular radius > 40 Å, indomethacin reduces this abnormal permeability. In contrast to the findings of others, a similar effect on the clearance quotient IgG/albumin was not found. Hulme and Pessina (1975) described in normal rats an increased $C_{PVP} > 40$ Å under angiotensin infusion. Donker et al (1975) reported that indomethacin suppresses the volume regulatory increase of plasma renin activity in normal man. It is tempting to speculate, against this background, that the effect of indomethacin on glomerular permeability in the nephrotic syndrome is not due to an influence on glomerular disease, but to suppression of enhanced angiotensin activity.

The possible role of "fixed antigen" in the pathogenesis of immune complex glomerulonephritis. *B. Van Damme, G. J. Fleuren, W. W. Bakker, R. L. Vernier, Ph. J. Hoedemaeker. Department of Pathology, University of Groningen, Groningen, The Netherlands.* The role of circulating soluble immune complexes in the pathogenesis of immune complex disease and especially in immune complex glomerulonephritis is generally accepted. Experiments have shown that immune complexes formed in antigen excess are soluble and may be deposited in the glomerular basement membrane (GBM). Through binding and activation of complement components, the GBM may be damaged and inflammation will follow. To study immune complex glomerulonephritis, a model for this disease was developed in the rat through injection of rabbit antibodies directed against brush border antigens from the tubules of the rat kidney. This injection resulted in immediate localization of immune complex aggregates in the GBM of both kidneys. It was shown, however, that in this model immune complexes were formed in antibody excess. Immune complexes formed in this way, however, were not supposed to localize in the GBM, unless the antigen was already present in the glomeruli. Immunohistology at the light microscopic and the ultrastructural level showed that Fx1A-like antigens were present in the cell membranes of the glomerular epithelial cells, along the foot processes and in the slit pore membranes. Furthermore, it was shown that in absence of antigen, the presence of rabbit and anti-rat Fx1A antibodies resulted in the localization of immune complex aggregates in the GBM. This was demonstrated subsequently by "*ex vivo*" perfusion of the left kidney of a rat with buffer, rabbit anti-Fx1A antibody, and again buffer. Rat kidneys perfused with immune complexes and normal rabbit IgG, and likewise having immunohistologic examinations of the right nonperfused kidney, served as controls. From these results it was concluded that in this form of experimental glomerulonephritis, a "fixed antigen" played an important role in the pathogenesis. This new concept for the pathogenesis of immune complex glomerulonephritis might also be relevant for other forms of glomerulonephritis, including human membranous glomerulopathy.

Influence of sodium balance on the effects of angiotensin-II blockade with saralasin. *P. van Hoogdalem, A. J. M. Donker, and F. H. H. Leenen. Department of Internal Medicine, Division of Nephrology, State University of Groningen, and the Department of Cardiology, Medical Faculty, University of Utrecht, the Netherlands.* In patients with unilateral renovascular hypertension ($N = 8$), bilateral renovascular hypertension ($N = 4$), and essential hypertension ($N = 4$), the effects of angiotensin-II blockade with sar^1-ala^8-angiotensin-II (saralasin) on blood pressure, plasma renin activity (PRA), glomerular filtration rate (GFR), and effective renal plasma flow (ERPF) were studied, both on a normal sodium intake (100 mEq/day) and after sodium depletion. On normal sodium intake, saralasin induced a decrease in mean blood pressure of −8 mm Hg in the unilateral renovascular group, −6 mm Hg in the bilateral renovascular group, and an increase in mean blood pressure of + 3 mm Hg in the essential hypertensive group. Following sodium depletion, saralasin decreased mean blood pressure by −33 mm Hg, −35 mm Hg, and −18 mm Hg, respectively. The saralasin-induced decrease in blood pressure significantly correlated with the log of the initial PRA for all studies together and for the different subgroups separately. PRA increased during the blockade when blood pressure decreased. Saralasin infusion resulted in decreases in ERPF in all three hypertension subgroups, both on normal sodium intake and after sodium depletion. GFR decreased, related to the hypotensive effect of saralasin. It is concluded that the hypotensive action of saralasin closely correlates with the level of circulating PRA, independent of the etiology of the hypertension. The decrease in ERPF during infusion of saralasin could be related to the agonistic activity of saralasin, the hypotensive effect of saralasin, and/or the absence of a blocking action of i.v. administered saralasin on stimulation of the renal vascular receptors by endogenous angiotensin-II formed intrarenally.